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Trauma and depressive symptomatology in middle-aged persons at high risk of dementia : the PREVENT Dementia Study

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Abstract

Objective. Depression and trauma are associated with changes in brain regions implicated in Alzheimer's disease. The present study examined associations between childhood trauma, depression, adult cognitive functioning and risk of dementia.

Methods. Data from 378 participants in the PREVENT Dementia Study aged 40-59 years. Linear and logistic models were used to assess associations between childhood trauma, depression, dementia risk, cognitive test scores and hippocampal volume.

Results. Childhood trauma was associated with depression and reduced hippocampal volume but not current cognitive function or dementia risk. Poorer performance on a delayed face/name recall task was associated with depression. Childhood trauma was associated with lower hippocampal volume however poorer cognitive performance was mediated by depression rather than structural brain differences.

Conclusion. Depressive symptomatology may be associated with dementia risk via multiple pathways, and future studies should consider sub-types of depressive symptomatology when examining its relationship to dementia.

Introduction

Alzheimer's disease (AD) and depressive disorders were once considered to be mutually exclusive; the co-occurrence of depression and cognitive decline being termed 'pseudomentia' [1]. Depression is now known to be closely associated with AD, with a prevalence around 50% at diagnosis [2, 3] compared to 20-25% for the general elderly population [4]. A meta-analysis [5] based on prospective population studies and adjusting for multiple confounders has estimated that late-life depression increases 1.65 fold the risk of future dementia, and also increases the risk of progression from mild cognitive impairment to dementia.

A central problem has been that the underlying mechanism which links the two pathologies is still uncertain, and controversy continues as to whether depression is a risk factor for AD or a prodromal feature of the disease itself. There is strong evidence that depressive symptoms are a direct result of AD-related brain changes. Structural and functional brain changes show depression in AD to be related to disruption of frontal-striatal and sub-cortical limbic pathways, either due to grey matter loss [6] or white matter lesions [7] accompanied by serotoninergic deficiency and a dopamine-norepinepherine imbalance [8]. Other studies have reported associations with tau accumulation and amyloid metabolism [9-12]. Several epidemiological studies further suggest that depression onset occurs mostly in the few years preceding the diagnosis of AD dementia, and is therefore prodromal [12]. A comparison of familial AD mutation carriers with their non-carrier relatives found reduced depression scores in mutation carriers in the presymptomatic stages of the disease, but elevated levels in carriers once dementia symptoms emerged, suggesting depression may be a symptom of onset rather than a risk factor for AD [13].

On the other hand a meta-analysis of prospective studies showed an inverse association with proximity to dementia, suggesting it to be a risk factor rather than a prodrome [14], and a

post-mortem study of persons with current major depression found no association between AD neuropathology and cognitive loss [15] suggestive of independent aetiological processes.

Longer term prospective studies reaching back into the pre-clinical phases of AD, and the possible origin of the association, are lacking. A recent 10 year retrospective study of clinical and biomarker changes in persons with incident AD observed that depressive symptomatology was significantly higher ten years before dementia diagnosis, remaining at a stable level to up to diagnosis independently of changes in other AD markers [16]. This finding suggests the lack of a dose-response effect in the association between depression and biomarker changes, and that depression may pre-date brain changes in AD. Depression thus appears to be linked to, but not entirely explained by prodromal AD neurodegeneration. Moreover, depression may be the endpoint of multiple etiological pathways implicating different underlying neuropathological processes and having different associations with AD onset [17]. Research in this area should thus attempt to focus on more homogeneous sub-types of depression

Neurobiological studies have demonstrated that childhood maltreatment may alter brain development by programming the glucocorticoid, noradrenergic and vasopressin stress response systems to over-react to new stressors [18], thus rendering the individual increasingly vulnerable to psychiatric disorder. These effects appear to be long-lasting [19] inducing structural and functional changes, notably reduced development of the hippocampus and amygdala, and abnormal fronto-temporal electrical activity [18]. These brain structures having also been implicated in the aetiology of both depression and dementia, it is not surprising that child abuse has been associated with not only increased risk for life-time depression [20, 21] but also lower cognitive scores [22]. Several small clinical studies of young adult women with a history of physical and sexual abuse reported disorders of vigilance, memory and mathematical ability compared to controls [23-25].

Depression associated with childhood trauma may thus provide a clear-cut model of the association of a depression sub-type with AD.

The present study is primarily designed to determine whether the association between childhood trauma and poorer cognitive performance is directly due to trauma-related hippocampal volume or mediated by depression. It further seeks to establish whether the impact on cognition may be greater in persons at genetic risk of dementia, thereby increasing brain burden in the face of possible pre-clinical changes. A secondary aim is to develop a putative model of the associations between trauma, depression, cognitive performance and dementia risk which may guide future longitudinal studies. The study uses data from a cohort of middle-aged persons in which around half have a family history of dementia in whom pre-clinical hippocampal changes have already been detected [26].

The following hypotheses are examined:

(i) middle aged persons who have experienced childhood trauma will have higher rates of clinical depression than those who have not

(ii) middle-aged persons exposed to childhood trauma will have lower hippocampal volume

(iii) childhood trauma will be associated with current poorer cognitive function

(iv) cognitive performance will be poorest in persons with both a history of childhood trauma and a high dementia risk

METHODS

Subjects were recruited from the PREVENT Dementia study; a prospective population study enriched for dementia risk, with around half of the participants having a family history of dementia ~~designed to detect mid-life pre-clinical changes in persons at risk of later-life~~

~~dementia.~~ The protocol has been described in detail elsewhere [27].

http://bmjopen.bmj.com/cgi/content/full/bmjopen-2012-001893. Briefly participants were recruited through the dementia register database, the Joint Dementia Research website and information about the study on the Internet and in study presentations. The present study included 378 participants from West London, Oxford and Cambridge for whom base-line data was available and validated on all variables and of whom 203 have a parent with diagnosed AD, vascular or mixed dementia. Persons with a parent with diagnosed dementia were considered to be at increased risk of future dementia and current pre-clinical brain changes.

Trauma

Life-time trauma was assessed using the Life Stressor Checklist -Revised [28], a thirty item self-administered questionnaire which assesses age of occurrence, perceived level of danger and subsequent impact on everyday life in the past year. The DSM IV [29] criterion A for Post-Traumatic Stress Disorder (PTSD) was applied to individual responses to distinguish trauma from milder transient stressors (for example moving house) and events with low perceived level of threat . Absence of information on the presence of subsequent intrusive symptoms did not allow us to make a formal diagnosis of PTSD. The items retained in relation to Criterion A were death of some-one close, physical and emotional abuse, sexual abuse, rape, family violence, adoption, separation from parents, neglect. For this study the scale was not formally scored, but rather the reporting of any of these items with a high associated perceived level of danger and subsequent impact on everyday life in the past year was classed as a traumatic event. The group was further divided into those experiencing these events before and after age 16. Within the total sample, 73 participants (19.3%) had been exposed to traumatic events before the age of 16.

Depression

The Center for Epidemiologic Studies-Depression Scale (CES-D) [30] was used to detect high levels of depressive symptomatology. Depression has been treated as a dichotomous variable with cases being defined as a score above the 16 cut-off point of the CES-D or current treatment with an anti-depressant. Of the 378 participants examined, 64 (16.9%) had CES-D scores of 16 and over and a further 29 participants (7.7%) were receiving anti-depressant treatment.

Cognitive testing

COGNITO is a computerized neuropsychological battery [31], designed to examine information processing across a wide range of cognitive functions in adults of all ages. Tests are administered using a tactile screen to capture information processing time as well as response accuracy.

Ten cognitive summary variables from the COGNITO battery were considered as dependent variables:

1. Working memory: the simultaneous presentation of auditory and visual attention tasks assessed by subtracting the time taken in milliseconds on this double task from the visual task alone.
2. Narrative recall : total number of correct elements) on immediate recall of a story with a temporal progression requiring attention to macrostructure
3. Description recall : total number of correct elements recalled of a description without thematic progression requiring retention to microstructure and recall of spatial location. The narrative and description recall are similar in terms of word frequency in the language and syntactic structure
4. Implicit memory ; difference in the number of steps in the progressive build-up of names on the screen required for recognition between names never seen and number of names previously learnt in an immediate recall task

5. Name-face association:number of faces recognized after a delay from a series of 18 faces of which 9 have been previously shown with their corresponding names

6. Form perception : number of correct answers in the matching of complex forms to a multiple choice array

7. Form perception speed: mean time taken in milliseconds for each trial of [6]

8. Phoneme comprehension: number of correct responses in the matching of a word with an image presented as part of a multiple-choice array including semantic, morphologic and phonetic distractors

9. Phoneme comprehension speed: mean time taken in milliseconds to perform [8]

10. Verbal fluency: total sum of the number of words generated in 30 seconds using both a semantic (vegtables) and phonemic (letter P) cue.

Imaging

Participants underwent multimodal 3T structural MRI on a single scanner including volumetric T1-weighted scans (176 slices, 1.0 x 1.0 mm, 1.0 mm slice thickness, TR = 2300ms, TE = 2.98ms, flip angle 9°). Brain tissue segmentation into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) was performed using the Gaussian mixture model in VBM toolbox of SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The GM maps were then normalized using the DARTEL algorithm [32]. Hippocampal region of interests (ROIs) were selected using AAL atlas in MNI space [33], and then inverse normalized back to each subject's native space using the participant-specific diffeomorphic parameters estimated from the previous DARTEL procedure. The resulting ROIs were also masked using the thresholded GM probability maps (at threshold $p > 0.8$) before the total hippocampal volume was calculated. Finally in order to control for premorbid brain volume, the hippocampal volumes were normalized by the estimated total intracranial volume (ICV).

Statistical analyses

Cases of depression were firstly compared with non-cases using a Chi-squared test for categorical variables and Wilcoxon two-sample test for continuous variables. The covariates associated with depression with a p-value <0.10 (except anxiety and educational level due to collinearity with socio-economic class) were then entered in a logistic model with the sum of traumatic events.

A linear model adjusted for education, gender and age was used to test the association of continuous cognitive scores with depression or a score derived from the sum of traumatic events occurring before the age of 16 as well as with hippocampal volume. For two non-continuous cognitive scores (form matching and phoneme comprehension) a logistic model was used after dichotomization (poor performance being defined as <7 and <9 correct responses, respectively). A linear model adjusted for intra-cranial volume was also used to test the association of hippocampal volume with depression and traumatic event scores. This model was further adjusted for education, gender, age and depression. All the analyses were carried out using SAS, version 9.4.

Results

Trauma and depression

The association between depression and socio-economic and clinical characteristics is given in Table 1.

Table 1 Association between depressive symptomatology (CES-D) and clinical and socio-economic characteristics

	Depressive symptomatology		
	CES-D<16 and not treated (n=285)	CES-D≥16 or treated (n=93)	
	n (%)	n (%)	P-value[a]
Sex, female	197 (69.1)	66 (71.0)	0.74
Marital status			0.02
Married or living as a couple	223 (78.3)	61 (66.3)	
Educational level			0.06
College / university	204 (71.8)	57 (61.3)	
Living alone	37 (13.0)	17 (18.3)	0.20
Socio-economic class, n=358			0.04
- Higher managerial, administrative occupations	75 (27.6)	14 (16.3)	
- Lower managerial, administrative occupations	108 (39.7)	31 (36.0)	
- Intermediate occupations	31 (11.4)	17 (19.8)	
- Employers, own account, technical, routine occupation	30 (11.0)	16 (18.6)	
- Never worked or long-term unemployed	28 (10.3)	8 (9.3)	
BMI (kg/m^2)			0.09
Normal (<25)	115 (40.3)	26 (28.0)	

Overweight (25-30)	106 (37.2)	40 (43.0)	
Obese (≥30)	64 (22.5)	27 (29.0)	
Hypertension (treated or SBP>140)	44 (15.4)	22 (23.7)	0.07
Cardiovascular disease (declared)	24 (8.4)	10 (10.8)	0.50
Diabetes (treated or declared or glycemia>7mmol/l), n=377	8 (2.8)	8 (8.6)	0.02
Anxiety symptoms (Spielberger state scale >31)	71 (24.9)	51 (54.8)	<0.0001
Traumatic events at any age (at least 2 events)	60 (21.1)	41 (44.1)	<0.0001
Traumatic events before 16 years (at least 1 early event)	33 (11.6)	21 (22.6)	0.009
	Median (IQR)	Median (IQR)	P-value[b]
Age (years)	53 (47-56)	53 (49-56)	0.76
Hippocampal grey matter volume (mm^3), n=193	3689 (3525 -3951)	3681 (3428 -3949)	0.66
Intracranial volume (cm^3), n=193	1387 (1299 -1477)	1354 (1268 -1451)	0.22

[a] Chi square test

[b] Wilcoxon two-sample test

[c] with parental history of dementia.

BMI: Body mass index, CES-D: Center for Epidemiologic Studies Depression Scale, IQR: Interquartile range, SBP: Systolic blood pressure.

Of the 73 participants exposed to childhood trauma, 26 (35.6%) had a CES-D score of 16 and over or were currently being treated for depression. The association between childhood trauma and depressive symptomatology is significant ($p<0.009$). A multivariate logistic model with depression as the dependent variable was used to examine the association between number of traumatic events adjusted for marital status, SES, hypertension, diabetes and BMI (Table 2). Adjustment was not made for anxiety given the high correlation between performance on the depression and anxiety scales due to overlap in items and also probably high rates of mixed anxiety and depression in participants.

Table 2. Adjusted association between childhood trauma and depression (n=356)

	Odds Ratio[a]	95% Confidence Interval	P- value
Marital status: married or living as a couple	0.59	0.34 – 1.03	0.06
Socio-economic class			0.03
- Higher managerial, administrative occupations	1		
- Lower managerial, administrative occupations	1.57	0.76 – 3.20	
- Intermediate occupations, employers, own account, technical, routine occupation	2.94	1.40 – 6.17	
- Never worked or long-term unemployed	1.56	0.57 – 4.30	
BMI: Overweight or obese	1.62	0.91 – 2.87	0.10
Hypertension (treated or SBP>140)	1.19	0.62 – 2.31	0.60
Diabetes (treated or declared or glycaemia >7mmol/l)	2.03	0.58 – 7.18	0.27
Traumatic events before age 16 (at least one)	2.52	1.33 – 4.80	0.005

[a] Adjusted for other variables in the table

BMI: Body mass index, trauma, SBP: Systolic blood pressure.

Hippocampal volume

Structural imaging data was available for the West London centre only (n=193, see supplemental material, Table S1 for sub-sample description). Table 3 shows the associations adjusted for intracranial volume between hippocampal volume as the dependent variable and depression, total number of traumatic events, and traumatic events before the age of 16. Three linear models are presented showing the independent associations of depression, trauma at any age and childhood trauma with hippocampal volume.Table 3. Associations between hippocampal volume as the dependent variable and depression or traumatic events (separate linear models)

Independent variables	Hippocampal gray matter volume (mm^3)	
	β(SE)[a]	p-value
Depressive symptomatology (CES-D≥16 or treated)	44.47 (33.65)	0.19
Traumatic events at any age (at least two events)	-10.98 (31.68)	0.73
Trauma before 16 years (at least one event)	-90.52 (38.20)	0.02

[a] Adjusted for total intracranial volume

CES-D: Center for Epidemiologic Studies Depression Scale.

In the sub-sample with an MRI examination, 21 participants were treated with antidepressants. In order to control for any possible effect of treatment on brain volume we also conducted the analyses excluding participants undergoing treatment. The result did not change and the association with depression adjusted for ICV remained non-significant (p=0.23).

The association with trauma before age 16 remained significant when it was adjusted for intracranial volume, education level, gender and age (β(SE)= -93.4 (39.0); p=0.02) as well as when depression was further added to the model (β(SE)= -99.4 (39.0); p=0.01). The relationship with hippocampal volume is not altered with adjustment by depression.

Cognitive performance in middle age

The association between current cognitive performance based on sub-scores from COGNITO and traumatic events before age 16 was examined using a multivariate model adjusted by education level, gender and age (Table 4).

Table 4. Association between childhood trauma and current cognitive performance

	Exposure to traumatic event		
	Yes	No	

Dependent variables	Mean(SEM)[a] N=54	Mean (SEM)[a] N=323	P- value
Working memory: time difference between double task and simple task (milliseconds)	-414.3 (431.9)	25.2 (192.9)	0.33
Form matching: mean time for correct responses (milliseconds)	5781.9 (214.3)	5713.4 (95.7)	0.76
Phoneme comprehension: mean time for correct responses (milliseconds)	1556.7 (41.7)	1500.9 (18.64)	0.20
Name-face associations: number of names correctly recalled	4.71 (0.28)	5.05 (0.13)	0.24
Verbal fluency: number of correct answers	27.80 (0.89)	27.78 (0.39)	0.98
Narrative recall: number of correct answers	12.73 (0.61)	12.79 (0.27)	0.92
Descriptive recall: number of correct answers	11.70 (0.58)	12.42 (0.26)	0.24
Implicit Memory: difference between learnt and new items	1.20 (0.10)	1.03 (0.05)	0.13

[a] Adjusted for education level, gender and age.

The number of correct answers for form matching and phoneme comprehension was not statistically associated with traumatic events before 16 years, the adjusted odds ratio (95% confidence interval) of poor performances was equal to 0.82 (0.46 - 1.47) and 0.94 (0.50 – 1.76), respectively.

A significant association was found between depression and delayed recall of names (p=0.03) but not on the other cognitive measures (supplemental material tables S2 and S3). No significant association was found between hippocampal volume and cognitive measures (supplemental material tables S4).

Risk of dementia

In persons with a family history of dementia, depression prevalence was 25.6% compared to 23.6% in those without a family history (p=0.64). 11.3% of persons with a family history of dementia reported being exposed to childhood trauma compared to 17.8% without (p=0.07).

No interaction effect was found between parental history of dementia and depression in relation to cognition. The interaction for Name Recall is p=0.54.

Given the complexity of the observed associations we constructed an Association Graph (Figure 1) designed to facilitate understanding and provide a hypothetical basis for future research..

Discussion

This study aimed to determine whether persons with a history of childhood trauma may be at increased risk of both depression and loss of hippocampal volume in mid-life, which may in turn be associated with cognitive performance in persons at increased risk for dementia.

The estimated prevalence of clinically significant depression in this study, based on CES-D scores (16.9%) and current anti-depressant treatment (7.7%) was observed to be very high (24.6%) compared to 5.1% estimated for a similar age group in western countries using DSM IV/CIDI criteria [33]. The rate remains high even if treated depression is excluded on the basis that anti-depressants may have in some cases been prescribed for reasons other than depression. Although different measures of depression have been used, previous studies show high concordance between DSM major depression and the CES-D [34]. While increased rates of depression might have been expected within this cohort enriched for dementia risk, depression prevalence was not observed in this mid-life group to be associated with a family history of dementia. A third of the cohort were exposed to a traumatic event, and of these 18% experienced the trauma before the age of 16. We found

an association between history of trauma and both clinical-level depression and volume loss in the hippocampus. Lower hippocampal volume was observed to be specifically related to childhood trauma and not with trauma experienced at other ages.. This finding is consistent with previous observations that trauma has its greatest effect on brain development through alterations in Hypothalamic-Pituitary-Adrenal (HPA) axis functioning when occurring before full brain maturation [18, 19]. It also underscores the need for future research to consider the context and timing of traumatic incidents along developmental trajectories.

In this mid-life cohort we observed that severe childhood trauma is associated in mid-life with both higher rates of clinical depression and lower hippocampal volume. For those persons who have experienced childhood trauma who develop dementia in the future it may be postulated that lower volume will add to the burden of hippocampal loss associated with the dementia. We did not at this point, however, observe any association with current cognitive performance or increased dementia risk (family history), suggesting that the direction of causality is probably not persons with a family history of dementia being more vulnerable to early life trauma.

Investigations of the interaction between adverse childhood experiences with genetic risk factors for AD in regard to later-life cognitive deterioration have provided mixed findings [22, 35]. A study of childhood abuse and cognition in bipolar disorder has suggested the possibility of a gene-environment interaction implicating genes known to exert a neurotrophic effect in response to cellular injury [36] notably Apolipoprotein E (ApoE). Polymorphisms on the ApoE gene may thus induce compensatory neurite outgrowth and synaptogenesis following neuronal injury [37] and thus modulate the neurobiological impact of environmental trauma in children while having an adverse effect in later life. Furthermore HPA axis vulnerability to trauma may further be modulated by genetic and epigenetic factors [38,39]. Together these observations suggest a far more complex aetiological model than we have been able to explore here due to lack of statistical power.

Overall our findings would be consistent with the idea that depression may in some cases be an indicator of underlying HPA axis dysfunction or altered sensitivity due to early life trauma which has led to associated alterations to the hippocampus. While this cannot be seen in this mid-life cohort to be related to either cognitive functioning or dementia risk, hippocampal volume loss may add to the burden of later dementia-related pathology. The aetiology of depression appears in this case to be independent of that of dementia, as previously suggested by O'Brien et al. [15] in relation to post-mortem studies of AD neuropathology in depressed elderly.

Our etiological model based on cross-sectional data suggests that childhood trauma is associated with both higher rates of depression and lower hippocampal volume. Poorer performance on an episodic memory test is associated with trauma but mediated by depression rather than hippocampal volume. Thus the relationship of depression to dementia risk in persons experiencing childhood trauma appears to be neither a risk factor nor a prodromal feature of the disease but that of a co-morbidity which could potentially add to brain burden..

It is important to note, however, that only 15% of persons at high AD risk experienced severe early-life trauma. Thus, even if our hypothesis is correct it will only concern a small proportion of dementia cases. There has been an underlying assumption in most previous studies of depression and AD that depression is a single clinical entity [3-6] despite well-documented variability in age of onset, precipitating factors, clinical profiles, genetic risk, associated pathologies and treatment response. Our findings do not preclude the possibility of other depression sub-types being linked to AD by alternative mechanisms. The importance of this study lies in the demonstration that depressive symptomatology may be present in persons at high risk for dementia via multiple pathways, and suggest that future studies should consider more carefully the origins of depressive symptomatology when examining its relationship to dementia.

The strengths of the present study are the younger age of the dementia-risk cohort and the identification of a relatively homogeneous depression sub-group. On the other hand the data relies on subjective recall of traumatic events and lack of longitudinal data. Future studies from PREVENT will be able to further explore the hypotheses suggested in this study with a larger cohort, longitudinal data, direct measures of HPA axis functioning and AD biomarkers with a view to the identification of novel targets for therapeutic intervention in adults with a history of childhood maltreatment at high risk of dementia.

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Contributorship

KR designed the study and wrote the original draft of the manuscript, JOB, SL, SD, TW, CWR, SG commented on and added to the discussion sections, IC assisted in the design of the study, carried out the statistical analyses and the writing up of results.

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Competing Interests

The authors have no conflict of interest to declare

Ethics Approval

NHS Research Ethics Committee London Camberwell St-Giles

(REC reference: 12/LO/1023).

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